Article

The relationship between BMI and insulin resistance and progression from single to multiple autoantibody positivity and type 1 diabetes among TrialNet Pathway to Prevention participants

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ABSTRACT

Aims/hypothesis The incidence of type 1 diabetes is increasing at a rate of 3-5% per year. Genetics cannot fully account for this trend, suggesting an influence of environmental factors. The accelerator hypothesis proposes an effect of metabolic factors on type 1 diabetes risk. To test this in the TrialNet Pathway to Prevention (PTP) cohort, we analysed the influence of BMI, weight status and insulin resistance on progression from single to multiple islet autoantibodies (Aab) and progression from normoglycaemia to diabetes.

Methods HOMA1-IR was used to estimate insulin resistance in Aab-positive PTP participants. Cox proportional hazards models were used to evaluate the effects of BMI, BMI percentile (BMI%), weight status and HOMA1-IR on the progression of autoimmunity or the development of diabetes.

Results Data from 1,310 single and 1,897 multiple Aab-positive PTP participants were included. We found no significant relationships between BMI, BMI%, weight status or HOMA1-IR and the progression from one to multiple Aabs. Similarly, among all Aab-positive participants, no significant relationships were found between BMI, weight status or HOMA1-IR and progression to diabetes. Diabetes risk was modestly increased with increasing BMI% among the entire cohort, in obese participants 13-20 years of age, and with increasing HOMA1-IR in adult Aab-positive participants.

Conclusions/interpretation Analysis of the accelerator hypothesis in the TrialNet PTP cohort does not suggest a broad influence of metabolic variables on diabetes risk. Efforts to identify other potentially modifiable environmental factors should continue.

Keywords: Accelerator hypothesis, BMI, Diabetes in childhood, HOMA1-IR, Insulin sensitivity and resistance, Pancreatic autoantibodies, Pathway to Prevention, Prediction and prevention of type 1 diabetes, TrialNet, Type 1 diabetes

Abbreviations

Aab	Autoantibodies
BMI%	BMI percentile
CDC	Centers for Disease Control and Prevention
DPT-1	Diabetes Prevention Trial of Type 1 Diabetes
GAD65	Glutamic acid decarboxylase 65
IA-2/ICA512	Islet-antigen 2
IQR	Interquartile range
PTP	Pathway to Prevention
ZNT8	Zinc transporter 8

Introduction

Type 1 diabetes is a heterogeneous disorder in which a primary or secondary islet insult renders the beta cell antigenic, leading to T-lymphocyte infiltration and production of pro-inflammatory cytokines such as IL-1β, TNFα and IFNγ. Over the past 30 years, there has been a global and largely unexplained increase in the incidence of type 1 diabetes, especially among younger populations [1, 2]. Between 1989-2003, the EuroDIAB study documented an annual increase in incidence of 5.4%, 4.3% and 2.9%

among children aged 0-4 years, 5-9 years and 10-14 years, respectively [3], while the SEARCH for Diabetes in Youth Study demonstrated a similar increase of 2.6% among American children from 2002-2009 [4]. High-risk *HLA* Class II alleles including *HLA-DR3* and *4* and *DQ2* and *8* increase the risk of type 1 diabetes [5], but the prevalence of these high-risk *HLA* alleles has remained largely stable [6]. Thus, inheritance alone is not likely to account for the rising prevalence of type 1 diabetes, suggesting roles for nongenetic and/or environmental factors.

Environmental influence has been well illustrated by twin studies [7] and reports showing that first-generation children of immigrant parents from regions with a low prevalence of type 1 diabetes experience a risk most similar to that in their new country [8]. Commonly implicated environmental factors include decreased rates of infection due to antibiotics and vaccination (the hygiene hypothesis) [9], viral infections [10], dietary factors and changes in the gut microbiome [11], decreased intake and endogenous synthesis of vitamin D [12], seasonality [13] and exposure to endocrine disrupting chemicals [14].

The accelerator or overload hypothesis is another highly favoured explanation and postulates that chronically increased beta cell secretory demand, occurring as a result of overnutrition, obesity and insulin resistance, may lead to activation of intrinsic beta cell stress pathways that either trigger autoimmunity through formation of neoantigens or act independently to accelerate autoimmune-mediated beta cell death [15]. Although weight loss is typically seen at the time of diabetes diagnosis, weight gain

in early life is suggested to be a risk factor both for the development of diabetes as well as for disease presentation at a younger age [16-19]. Moreover, rates of obesity have increased in children. For example, obesity amongst US children more than doubled in some age groups from 1976-1980 to 2009-2010 [20].

Data from the Diabetes Prevention Trial of Type 1 Diabetes (DPT-1), which served as the precursor to the Type 1 Diabetes TrialNet study, revealed a modest impact of metabolic variables on diabetes risk [21, 22]. However, a DPT-1 Risk Score, which includes BMI, has proven to be predictive of progression to diabetes [23-25]. In another analysis, data from over 9,000 German and Austrian children between the years 1990-2003 revealed higher BMI and weight in those diagnosed with diabetes than those in the control reference population [17].

Given this background, the goal of this study was to test the accelerator hypothesis within a contemporary international and mixed-age cohort at increased genetic risk of diabetes. Type 1 Diabetes TrialNet is an ongoing clinical trial with centres located in the USA, Canada, the UK, Germany, Italy, Australia and New Zealand. In the TrialNet Pathway to Prevention (PTP) cohort, blood relatives of individuals with type 1 diabetes are screened for the presence of pancreatic islet autoantibodies (Aabs). Those positive for at least one Aab are then followed up longitudinally for the development of additional islet Aabs, dysglycaemia and diabetes. By use of data derived from the TrialNet PTP cohort, we tested whether BMI, obesity or overweight status and/or insulin resistance as measured by HOMA1-IR were related to progression of autoimmunity (as

measured by the conversion from single to multiple Aab status) or ultimately to the progression to type 1 diabetes.

Methods

Participants and follow-up Details of the enrolment criteria for entry into the TrialNet PTP cohort, which began in 2001, have been described previously [26]. In brief, nondiabetic first-degree relatives (ages 1-45 years) and second or third-degree relatives (ages 1-20 years) of individuals with type 1 diabetes were screened for the presence of pancreatic islet Aabs in a stepwise fashion. Participants were tested first for the presence of GAD65 (glutamic acid decarboxylase 65), insulin, or IA-2/ICA512 (islet-antigen 2) Aabs, followed by measurement of islet cell Aabs (ICA) or zinc transporter 8 (ZnT8) Aabs if any one initial test was positive [27]. Measurement of ZnT8 was initiated in 2004 [28], and was consistently measured in the PTP cohort starting in 2012. Confirmed Aab positive (Aab+) individuals were invited to participate in longitudinal observation with either semi-annual or annual monitoring. The strategy for monitoring included measurement of height and weight, and performance of a standard protocol OGTT [29].

A total of 134,937 eligible individuals were screened from 2001 through June 30, 2014 (electronic supplementary material [ESM] Fig. 1). A total of 2,299 individuals were confirmed on repeat testing to be single Aab+ (GAD65, insulin or IA-2/ICA512), while a total of 2,960 individuals were identified to be multiple Aab+. Analyses presented here

focus on those who had at least one monitoring visit (1,310 single Aab+ and 1,897 multiple Aab+ individuals). Participants who later entered prevention trials were censored at the time of initial enrolment into the prevention trial. All participants provided written informed consent prior to commencement of data collection. The study was approved by the ethical boards of all participating institutions and was conducted according to standards established by the Declaration of Helsinki.

Laboratory analyses Aab status was assessed using procedures outlined by the Diabetes Antibody Standardization Program and described in detail in previous publications [30]. Glucose was measured using the glucose oxidase method [31]. Insulin was initially measured by radioimmunoassay [32]; however, this was transitioned to a TOSOH AIA (Automated Immunoassay) (San Francisco, CA, USA) in 2009-2010. HOMA1-IR was calculated as described previously using values obtained from the first OGTT performed during the initial monitoring visit [21]. BMI was calculated for each participant using data from the first monitoring visit. For children and adolescents ≤19 years of age, BMI z scores (SDs) were calculated using the Centers for Disease Control and Prevention (CDC) SAS program for the 2000 CDC growth charts (www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm); *z* scores were then used to calculate BMI percentile values using the lambda-mu-sigma (LMS) method as previously described [33]. BMI percentile values for age 20 years were applied to all individuals ≥ 20 years of age. BMI data was missing for 102 (7.8%) of single Aab+

participants and 201 (10.6%) of participants with multiple Aabs. BMI, BMI percentile (BMI%) and HOMA1-IR were defined as continuous variables, whereas BMI/BMI% values were also analysed as categorical variables. BMI category divisions included underweight (BMI <18.5 kg/m^2 and/or BMI% <5%), normal (BMI ≥ 18.5 kg/m^2 and < 25 kg/m^2 and/or BMI percentile ≥ 5% and < 85%), overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2 and/or BMI percentile ≥ 85% and < 95%) and obese (BMI ≥ 30 kg/m^2 and/or BMI percentile ≥95%). Diabetes was diagnosed according to American Diabetes Association criteria (confirmed fasting plasma glucose ≥ 7.0 mmol/L, random glucose ≥ 11.1 mmol/L, or $HbA_{1c} \geq$ 6.5% [48 mmol/mol]) [34].

Statistical methods Categorical variables were compared among groups by Pearson's χ^2 tests or Fisher Exact tests when cell sizes were insufficient. Continuous variables were summarised either by mean ± SD or median and interquartile range (IQR). Two-sample *t* tests were used to compare the difference of means for these variables between groups. The association of HOMA1-IR, BMI, BMI percentile and time to progression from single to multiple Aab conversion or time to progression to a clinical diagnosis of type 1 diabetes was adjusted for potential confounders using the multivariate Cox proportional hazards model. Assumptions for proportionality of hazards were tested for in these models [35], and age at the initial screen, sex, *HLA* risk, relationship to proband, and race were adjusted for in the model. Age groups were divided into three groups: <13 vs 13-20 vs >20 years old. Interactions between

metabolic variables and age groups were also assessed using first-order interaction terms in the Cox models as well as in stratified analyses based on age groups. All tests of significance were two-sided, where p values < 0.05 were considered to be statistically significant. Statistical analyses were performed with SAS Version 9.2 (Cary, NC, USA).

Results

Anthropometric measurements and metabolic data were collected on PTP participants confirmed to have a single Aab (n=1,310) and those with multiple Aabs (n=1,897) and compared between groups. Participants in both the single and multiple Aab+ groups were predominantly white (82.6% and 86.7%, respectively), non-Hispanic (80.1% and 85.5%, respectively) and first-degree relatives of probands. There was a significantly higher percentage of females in the single Aab+ cohort (60.8%) vs the multiple Aab+ cohort (49.5%). *HLA DR3* or *DR4* was present in 66.9% of single Aab+ and 71.9% of multiple Aab+ individuals (Table 1).

Individuals confirmed as single Aab+ were older at initial screening than multiple Aab+ participants (p<0.001). Of the single Aab+ group, 5.2% (n=69) of participants were underweight, 46.6% (n=611) were categorised as normal weight, 21.2% (n=278) were overweight and 19.1% (n=250) were obese. Of the multiple Aab+ group, 6.9% (n=131) were underweight, 53.8% (n=1020) were normal weight, 14.9% (n=282) were overweight and 13.9% (n=263) were obese. Single Aab+ individuals also had higher HOMA1-IR values than those with multiple Aabs (p=0.001; Table 1).

BMI/BMI percentiles were next analysed as continuous variables and participants were also stratified by weight category as outlined in the Methods. Characteristics of obese and nonobese (underweight, normal weight and overweight) PTP participants are shown in Table 2. Consistent with relationships shown in Table 1, a higher percentage of obese individuals were single Aab+ compared with nonobese individuals (48.7% vs 40.1%, respectively; p=0.0004). Obese participants tended to be older at initial screening than nonobese participants (median age: 28.2 vs 11.9 years, respectively; p<0.001). However, overall age ranges were overlapping for obese and nonobese participants: 1.30–45.99 years vs 1.01–46.59 years, respectively (ESM Table 1).

Among the 1,310 confirmed single Aab+ PTP participants who had at least one monitoring visit, 288 (22.0%) individuals progressed to multiple Aab+ status during follow-up. The median follow-up time of single Aab+ individuals was 2.5 years (IQR 1.32-4.38 years). Univariate analysis confirmed an increased risk of progression to multiple positive Aabs or diabetes in younger, male individuals [36]. Interestingly, univariate analysis also suggested a protective effect of overweight status on the risk of progression to multiple Aabs (HR 0.64, 95% CI 0.46, 0.88; p=0.01). Similarly, higher BMI and BMI percentiles were also associated with a moderately decreased risk of progression to multiple Aabs (p<0.01). No other significant associations were seen between metabolic variables and progression to multiple Aabs in univariate analysis (Table 3).

Cox proportional hazards models were used next to evaluate the influence of HOMA1-IR, BMI, BMI percentile and BMI category on the progression from single to multiple Aabs after adjusting for age, sex, *HLA* risk, relationship to proband and race (Table 4). In the adjusted analysis, the protective effect of BMI or overweight status did not persist, and no statistically significant relationships were revealed between BMI (p=0.73), BMI percentile (p=0.27), overweight (p=0.34) or obese (p=0.96) status, or HOMA1-IR (p=0.47) and risk of progression from single to multiple Aab status. Similarly, no relationship was seen between underweight status and this endpoint (p=0.70).

Among 3,207 single or multiple Aab+ PTP participants, 647 (20.2%) individuals progressed to diabetes. Type 1 diabetes developed in 579/1,897 (30.5%) individuals with multiple Aabs and only 68/1,310 (5.2%) individuals with a confirmed single Aab over the median follow-up time of 2.31 years (IQR 0.97-4.20 years). Individuals positive for *HLA DR3* and *DR4* demonstrated the expected increase in risk of progression to diabetes (Table 3). Univariate analysis suggested an increased risk of underweight status (HR 1.90, 95% CI 1.46, 2.47), but again a protective effect of obese status on the risk of progression to diabetes as an outcome (HR 0.77, 95% CI 0.60, 0.98; p=0.032). Higher BMI was also found to be associated with a decreased risk of progression to diabetes in univariate analysis (HR 0.93, 95% CI 0.92,0.95; p<0.001). However, after adjusting for age, sex, race, relationship to proband and *HLA* risk, no significant associations between BMI (p=0.29), underweight (p=0.96), overweight (p=0.08) or obese status (p=0.10), or HOMA1-IR (p=0.56) and progression to diabetes in single and

multiple Aab+ participants were revealed (Table 4). This analysis revealed a modestly increased risk of diabetes with increasing BMI% (HR 1.004, 1.00-1.01; p=0.04). Furthermore, there was a significant interaction between obesity and age group in relation to time to type 1 diabetes (p=0.04); i.e. there was a differential impact of obesity on time to type 1 diabetes between age groups. Specifically, obesity significantly increased the risk of type 1 diabetes in individuals who were 13-20 years old (HR=2.06, p=0.045; Table 5).

We next stratified participants by Aab status, and Cox proportional hazards models were used to analyse progression to type 1 diabetes as an outcome. Again, we found no associations between BMI, BMI percentile, obesity or overweight status, or HOMA1-IR and time to progression to diabetes when single Aab+ individuals and multiple Aab+ individuals were analysed separately (Table 5).

Finally, Aab+ individuals were stratified by age, such that age at initial screening was categorised into three groups: <13 vs 13 to 20 vs over 20 years of age. Subgroup analysis revealed that obese participants aged 13-20 years displayed a significantly increased risk of progression to diabetes compared with age-matched normal-weight participants (HR 2.06, 95% CI 1.02, 4.19; p=0.045; Table 5). Furthermore, increasing HOMA1-IR was associated with a moderate risk of progression to diabetes in adult Aab+ individuals who were >20 years of age (HR 1.17, 95% CI 1.05,1.31; p=0.004). We further evaluated changes in HOMA-IR levels from baseline to the last assessment performed before diabetes diagnosis. Interestingly, there was a significantly larger

change in HOMA-IR values from baseline among those who developed type 1 diabetes compared to those who remained diabetes free in the overall cohort (0.23 ± 1.28 vs 0.03 ± 1.36; p<0.001). When only individuals >20 years of age were considered, the change in HOMA-IR for those who developed diabetes was 0.76 ± 2.39 vs a change of 0.02 ± 0.96 in those who remained diabetes free; p<0.001).

Discussion

Here, we tested whether metabolic variables were related to progression from one to multiple Aabs or ultimately to type 1 diabetes as an outcome within the TrialNet PTP cohort. Our analysis failed to reveal a significant relationship between BMI, BMI percentile, weight status or insulin resistance and conversion from one to multiple islet Aabs. Similar findings were seen in the analysis between metabolic factors and progression to diabetes. The only exception was that increasing BMI% was associated with an increased risk of progression to type 1 diabetes in single and multiple Aab+ participants (Table 3). However, this effect was quite modest (HR 1.004, 95% CI 1.00, 1.01; p=0.04). Further analysis following stratification by age revealed that obesity was significantly associated with increased diabetes risk among individuals 13-20 years of age (HR 2.03; p=0.049), whereas increasing HOMA-IR was associated with a moderately increased risk of diabetes in adult Aab+ individuals who were >20 years of age (HR 1.17; p=0.004).

The accelerator hypothesis has been advanced for a number of reasons. Recent data demonstrate a steady increase in the incidence of type 1 diabetes of approximately 3-5% per year. Interestingly, recent studies have also revealed decreased representation of high-risk *HLA* alleles among participants with new-onset type 1 diabetes, with increasing penetrance in medium, low and very low risk genotypes [6, 37], suggesting an influence of environmental factors, such as weight status or insulin resistance. Indeed, rates of obesity have increased among all age groups over the past 20-30 years [20]. However, the prevalence of obesity has begun to plateau in some populations [38]. By contrast, the incidence of type 1 diabetes continues to increase, especially among the very young [39].

Analysis of the effect of metabolic factors in other cohorts has also been inconsistent. The DPT-1 study served as the precursor to the current TrialNet study. Results from DPT-1 showed that both HOMA1-IR and the ratio of the first phase insulin response to HOMA1-IR were significantly associated with progression to diabetes among Aab+ individuals. In contrast to DPT-1, our findings suggest that HOMA1-IR was not broadly associated with diabetes risk, but rather that increasing HOMA1-IR was associated with a moderately increased risk among older, adult individuals. Compared with DPT-1, which only screened participants in the US, TrialNet is an international study and includes more female participants and older relatives [31]. Interestingly, at least for participants $\geq$ 13 years of age, BMI was significantly higher in PTP participants than those enrolled in DPT-1 [31].

The German BABYDIAB study enrolled children born to parents with diabetes and also failed to reveal any relationship between BMI and HOMA1-IR and the development of islet autoimmunity [40]. In the US Diabetes Autoimmunity Study in the Young (DAISY), increased height growth velocity from age 2 years was associated with the development of islet autoimmunity; however, there was no association with BMI or weight [41]. Likewise, a recent analysis of the Pittsburgh cohort found no relationship between obesity and insulin resistance and the number of Aabs, progression to diabetes, or acceleration of diabetes at a younger age [42]. Data from the US SEARCH study [18], the Philadelphia Pediatric Diabetes Registry [43], and national Catalan [44] and Australian cohorts [45] have also failed to support the accelerator hypothesis. The Australian BABYDIAB study did uncover an association between BMI at age 2 years and islet autoimmunity, but progression to diabetes in this cohort was not assessed [46]. Thus, the preponderance of data from multiple cohorts, including ours, does not provide strong support for the accelerator hypothesis.

A number of important limitations illustrate the inherent difficulty of studying this question. First, participants are recruited into TrialNet and other cohorts based on having a blood relative with type 1 diabetes, such that genetic factors may play a predominant role. Indeed, high-risk *HLA* alleles were present in about two-thirds of our study population. Genome-wide association studies have identified additional risk loci including non-*HLA* genes such as *INS*, *PTPN22*, *GLIS3*, *IL2RA*, *UBASH3A* and *HLA* Class I alleles that confer a lower risk of progression to diabetes [47, 48]. Thus,

recruitment of future natural history studies may benefit from active incorporation of individuals with more diverse and lower risk *HLA* and non-*HLA* alleles, such that an influence of environmental factors may be more pronounced.

HOMA1-IR was used in our studies and many others and serves as a surrogate marker of insulin resistance. Practically incorporating a gold standard measure, such as the hyperinsulinaemic-euglycaemic clamp, into large epidemiological studies would be more precise but challenging and expensive. Moreover, the average BMI of the PTP cohort was 22 kg/m^2, and obese participants tended to be older. Thus, it would be useful to test our findings in a cohort enriched for younger participants with higher BMI values. In addition, BMI and HOMA1-IR were collected at baseline, but perhaps assessment of dynamic changes in metabolic variables would provide additional insight into how these factors influence risk [49]. To this end, we explored changes in HOMA1-IR and the development of diabetes, and interestingly found that individuals who progressed to diabetes exhibited a significantly larger increase in HOMA1-IR values compared with those who remained diabetes free.

Finally, our results revealed a significantly increased risk of diabetes among obese, peripubertal individuals aged 13-20 yrs. The incidence of type 1 diabetes exhibits a peak around the pubertal transition, a time associated with changes in secretion patterns of sex hormones that also impact insulin sensitivity. Thus, it is biologically plausible that obesity may compound these effects, and further increase diabetes risk in the peripubertal/early post-pubertal age group [41]. Whereas Tanner

staging was not collected for our study participants, data of this type would help better contextualise these findings [50].

In summary, we failed to demonstrate a pervasive effect of metabolic factors on diabetes risk. However, our results support a common sense approach towards maintenance of normal weight status in at-risk Aab+ individuals, especially during the pubertal transition and in older participants to avoid the development of insulin resistance. These data also suggest that efforts to identify other potentially modifiable environmental or lifestyle risk factors for type 1 diabetes should continue.

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Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement

FAM, CEM, PX and SG conceptualised the analysis, analysed and interpreted data, and wrote the manuscript. LAD, CJG, JSB, JMS and AP conceptualised the analysis, interpreted data and reviewed/edited the manuscript. CEM is the guarantor of this work, and all authors provided final approval of the manuscript prior to publishing.

Table 1 PTP participant characteristics by autoantibody status

Characteristics	Group 1:single Aab+ (n=1,310)	Group 2:multiple Aab+ (n=1,897)	Group 1 vs group 2 (*p* value)
Age at initial screening			
Median (Q1–Q3)	23.28 (10.51–38.14)	11.88 (7.52–19.44)	<0.001
Mean (SD)	23.66 (14.45)	14.8 (11.55)	<0.001
Sex, n (%)			<0.0001[b]
Male	508 (38.78)	947 (49.92)	
Female	797 (60.84)	939 (49.50)	
Unknown/not reported	5 (0.38)	11 (0.58)	
Race, n (%)			0.01[b]
White	1082 (82.60)	1645 (86.72)	
African-American	30 (2.29)	59 (3.11)	
Asian	20 (1.53)	21 (1.11)	
American Indian	4 (0.31)	4 (0.21)	
Native Hawaiian, Pacific Islander	3 (0.23)	2 (0.11)	
Other	134 (10.23)	133 (7.01)	
Unknown/not reported	37 (2.83)	33 (1.74)	
Ethnicity, n (%)			<0.001[b]
Hispanic	203 (15.50)	187 (9.86)	
Non-Hispanic	1049 (80.08)	1622 (85.50)	
Unknown/not reported	58 (4.43)	88 (4.64)	
Relationship to proband, n (%)			<0.001[b]
Sibling	472 (36.03)	1103 (58.14)	
Offspring	213 (16.26)	378 (19.93)	
Parent	482 (36.79)	245 (12.92)	
Other	128 (9.77)	142 (7.49)	
Unknown/not reported	15 (1.15)	29 (1.53)	
Number of positive Aabs at initial screen, n (%)			
0	0 (0.00)	0 (0.00)	
1	1310 (100.00)	0 (0.00)	
2	0 (0.00)	774 (40.80)	
3	0 (0.00)	556 (29.31)	
4	0 (0.00)	392 (20.66)	
5	0 (0.00)	175(9.23)	
HLA, n (%)			<0.001[b]
DR3 and *DR4* absent	243 (18.55)	215 (11.33)	
DR3 or *DR4* present	876 (66.87)	1364(71.90)	
Unknown/not reported	191 (14.58)	318 (16.76)	
Weight category, n (%)			<0.001[b]
Underweight	69 (5.27)	131 (6.91)	
Normal	611 (46.64)	1020 (53.77)	
Overweight[a]	278 (21.22)	282 (14.87)	
Obese[a]	250 (19.08)	263 (13.86)	
Unknown	102 (7.79)	201 (10.60)	
Weight (kg) mean (SD)	61.05 (27.26)	47.65 (26.67)	<0.001
Height (cm) mean (SD)	155.9 (22.55)	145.14 (26.02)	<0.001
BMI (percentile) mean (SD)	67.75 (28.33)	63.05 (29.0)	<0.001
HOMA1-IR mean (SD)	1.99 (2.08)	1.75 (1.46)	<0.001

[a]Obese defined as a BMI ≥30 kg/m^2 and/or BMI% ≥95%; overweight defined as BMI ≥25 kg/m^2 and <30 kg/m^2 and/or BMI% ≥85% and <95%; normal weight defined as BMI ≥18.5 kg/m^2 and <25 kg/m^2 and/or BMI% ≥5% and <85%; underweight defined as BMI ≤18.5 kg/m^2 and/or BMI% ≤5%. Reference group defined as normal weight

[b] χ^2 *p* values, not including unknown/reported participants

Table 2 PTP participant characteristics by BMI category

Characteristic	Obese participants[a] (n=513)	Non-obese participants[a] (n=2,391)	Obese vs non-obese (*p* value)
Age at initial screening			<0.001
Median (Q1–Q3)	28.24 (11.07–38.87)	11.91 (7.29–23.99)	
Mean (SD)	25.37 (14.34)	16.75 (12.81)	
Sex, n (%)			0.44
Male	227 (44.25)	1103 (46.13)	
Female	285 (55.56)	1277 (53.41)	
Unknown/not reported	1 (0.19)	11 (0.46)	
Race, n (%)			0.009
White	407 (79.34)	2053 (85.86)	
African-American	22 (4.29)	60 (2.51)	
Other	63 (12.28)	234 (9.79)	
Unknown/not reported	21 (4.09)	44 (1.84)	
Number of positive Aabs at initial screen, n (%)			0.0004
1	250 (48.73)	958 (40.07)	
2+	263 (51.27)	1433 (59.93)	

[a]Obese defined as a BMI ≥30 kg/m^2 and/or BMI% ≥95%; non-obese includes underweight/normal/overweight participants

Table 3 Univariate results of possible risk factors with progression outcomes

Factor	Time to progression to multiple Aab+			Time to progression to type 1 diabetes	
	HR (95% CI)	*p* value		HR (95% CI)	*p* value
Age at initial screening	0.98 (0.97, 0.99)	0.001		0.95 (0.947, 0.96)	<0.001
Sex					
Female (ref)					
Male	1.36 (1.08, 1.71)	0.01		1.34 (1.15, 1.57)	<0.001
HLA (if *DR3* or *DR4*)					
Absent (ref)					
Present	1.38 (0.99, 1.93)	0.06		1.96 (1.45, 2.65)	<0.001
Relationship to proband					
Non-first degree (ref)					
First degree	1.52 (0.98, 2.37)	0.06		1.02(0.77, 1.35)	0.90
Race					
White (ref)					
African-American	0.68 (0.28, 1.66)	0.40		1.10(0.68, 1.78)	0.71
Other	0.63 (0.42, 0.92)	0.02		0.74(0.57, 0.98)	0.03
Aab positivity					
Single positive (ref)					
Multiple positive				8.31(6.46, 10.69)	<0.001
BMI categories					
Normal (ref)					
Underweight	0.89 (0.52, 1.09)	0.66		1.90(1.46, 2.47)	<0.001
Overweight[a]	0.64 (0.46, 0.88)	0.01		0.80(0.64, 1.00)	0.054
Obese[a]	0.80 (0.59, 1.09)	0.16		0.77(0.60, 0.98)	0.032
BMI (kg/m^2)	0.97 (0.95, 0.99)	0.01		0.93(0.92, 0.95)	<0.001
BMI%	0.994 (0.99, 0.99)	0.01		1.00(0.99, 1.01)	0.14

HOMA1-IR	1.02 (0.95, 1.09)	0.67		0.95(0.90, 1.02)	0.14

[a]Obese defined as a BMI ≥30 kg/m^2 and/or BMI% ≥95%; overweight defined as BMI ≥25 kg/m^2 and <30 kg/m^2 and/or BMI% ≥85% and <95%; normal weight defined as BMI ≥18.5 kg/m^2 and <25 kg/m^2 and/or BMI% ≥5% and <85%; underweight defined as BMI ≤18.5 kg/m^2 and/or BMI% ≤5%. Reference group defined as normal weight

Table 4 Multivariate analysis of progression of islet autoimmunity and progression to type 1 diabetes

Variable	Time to progression to multiple Aabs[b]			Time to progression to type 1 diabetes[b]	
	HR (95% CI)[c]	p value		HR (95% CI)[c]	p value
BMI (kg/m^2)	1.00 (0.97, 1.02)	0.73		1.01 (0.99, 1.03)	0.29
BMI%	1.00 (0.99, 1.01)	0.27		1.004 (1.0002, 1.007)	0.04
HOMA1-IR	0.96 (0.87, 1.07)	0.47		1.02 (0.95, 1.09)	0.56
BMI categories[a]					
Underweight vs normal	0.89 (0.50, 1.60)	0.70		0.99 (0.73, 1.35)	0.96
Overweight vs normal	0.84 (0.58, 1.21)	0.34		1.25 (0.98, 1.60)	0.08
Obese vs normal	1.01 (0.70, 1.45)	0.96		1.26 (0.96, 1.65)	0.10
Obese vs non-obese (overweight/normal/underweight)	1.20 (0.84, 1.69)	0.34		1.20 (0.92, 1.56)	0.18

[a]Obese defined as a BMI ≥30 kg/m^2 and/or BMI% ≥95%; overweight defined as BMI ≥25 kg/m^2 and <30 kg/m^2 and/or BMI% ≥85% and <95%; normal weight defined as BMI ≥18.5 kg/m^2 and <25 kg/m^2 and/or BMI% ≥5% and <85%; underweight defined as BMI ≤18.5 kg/m^2 and/or BMI% ≤5%. Reference group defined as normal weight

[b]Cox proportional hazard model adjusted by age at initial screen, sex, *HLA* risk, relationship to proband and race
[c]HR defined per every one unit increase in measure for each continuous (BMI, BMI% and HOMA1-IR) variable

Table 5 Cox proportional hazard model of type 1 diabetes development with stratification by number of positive Aabs and age at initial screening

Variable	HR (95% CI)	*p* value[b]
Aab status[b]		
Confirmed single Aab+ (n=1,310)		
BMI (kg/m^2)	1.01 (0.96, 1.07)	0.74
BMI%	1.01 (0.99, 1.02)	0.24
Obese vs normal[a]	1.17 (0.54, 2.55)	0.68
Overweight vs normal[a]	1.20 (0.57, 2.50)	0.63
Underweight vs normal[a]	1.32 (0.40, 4.47)	0.65
Obese vs non-obese[a]	1.09 (0.53, 2.23)	0.82
HOMA1-IR	1.09 (0.93, 1.28)	0.30
Multiple Aab+ (n=1,897)		
BMI (kg/m^2)	1.01 (0.99, 1.04)	0.31
BMI%	1.00 (0.99, 1.01)	0.06
Obese vs normal[a]	1.31 (0.97, 1.75)	0.08
Overweight vs normal[a]	1.26 (0.96, 1.64)	0.09
Underweight vs normal[a]	1.07 (0.78, 1.47)	0.69
Obese vs non-obese[a]	1.24 (0.93, 1.64)	0.15
HOMA1-IR	1.05 (0.98, 1.13)	0.15
Age at initial screen[b]		
Age <13 years (n=1632)		
BMI%	1.01 (0.99, 1.01)	0.06
Obese vs normal[a]	1.28 (0.91, 1.80)	0.16
Overweight vs normal[a]	1.28 (0.95, 1.74)	0.11
Underweight vs normal[a]	1.00 (0.72, 1.38)	0.998
Obese vs non-obese[a]	1.23 (0.88, 1.71)	0.23
HOMA1-IR	0.99 (0.90, 1.09)	0.83
Age 13-20 years (n=532)		
BMI%	1.00 (0.99, 1.01)	0.65
Obese vs normal[a]	2.06 (1.02, 4.19)	0.045
Overweight vs normal[a]	1.37 (0.70, 2.67)	0.36
Underweight vs normal[a]	1.43 (0.33, 6.09)	0.63
Obese vs non-obese[a]	1.92 (0.96, 3.84)	0.064
HOMA1-IR	1.11 (0.96, 1.28)	0.15
Age $\geq$ 20 years (n=1,039)		
BMI (kg/m^2)	0.99 (0.95, 1.03)	0.57
BMI%	1.00 (0.99, 1.01)	0.80
Obese vs normal[a]	0.83 (0.45, 1.51)	0.53
Overweight vs normal[a]	0.97 (0.54, 1.77)	0.93
Underweight vs normal[a]	NA	NA
Obese vs non-obese[a]	0.83 (0.48, 1.45)	0.52
HOMA1-IR	1.17 (1.05, 1.31)	0.004

[a]Obese defined as a BMI ≥30 kg/m^2 and/or BMI% ≥95%; overweight defined as BMI ≥25 kg/m^2 and <30 kg/m^2 and/or BMI% ≥85% and <95%; normal weight defined as BMI ≥18.5 kg/m^2 and <25 kg/m^2 and/or BMI% ≥5% and <85%;

underweight defined as BMI ≤18.5 kg/m^2 and/or BMI% ≤5%. Reference group defined as normal weight, and non-obese defined as underweight/normal/overweight

[b]Cox proportional hazard model adjusted by age at initial screen, sex, *HLA* risk, relationship to proband, race and number of Aabs at initial screen

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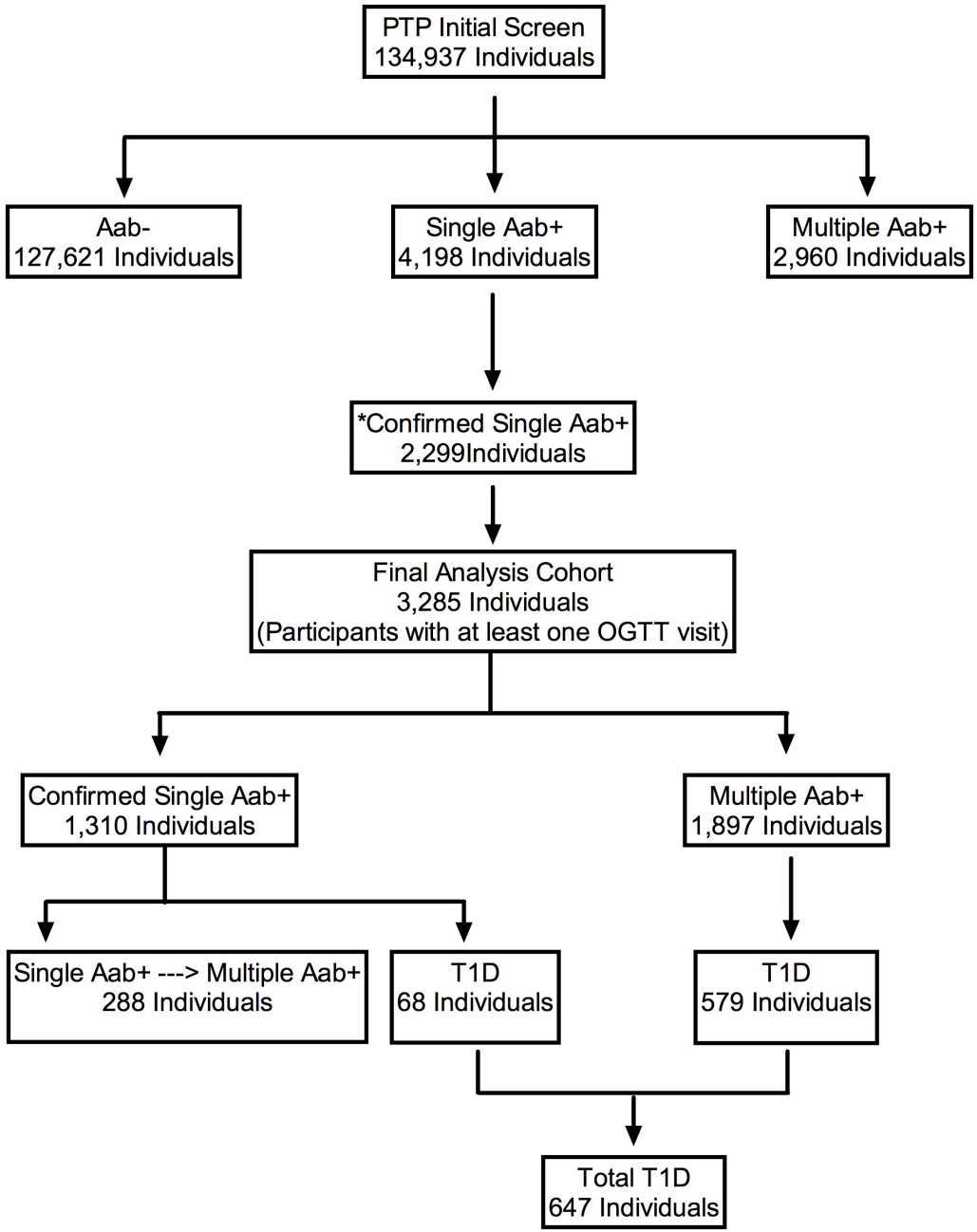
Supplemental Table 1: Univariate Results of Possible Risk Factors with Progression Outcomes

Factor	**Time to progression to multiple Aab +**		**Time to progression to type 1 diabetes**	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Age at initial screening	0.98(0.97-0.99)	*0.001*	0.95(0.947-0.96)	*<0.001*
Gender				
Female (ref)				
Male	1.36(1.08-1.71)	*0.01*	1.34(1.15-1.57)	*<0.001*
HLA (If DR3 or DR4)				
Absent (ref)				
Present	1.38(0.99-1.93)	*0.06*	1.96(1.45-2.65)	*<0.001*
Relationship to proband				
Non-first Degree (ref)				
First Degree	1.52(0.98-2.37)	*0.06*	1.02(0.77-1.35)	*0.90*
Race				
White (ref)				
African American	0.68(0.28-1.66)	*0.40*	1.10(0.68-1.78)	*0.71*
Other	0.63(0.42-0.92)	*0.02*	0.74(0.57-0.98)	*0.03*
Aab positivity				
Single positive (ref)				
Multiple positive			8.31(6.46-10.69)	*<0.001*
BMI categories[#]				
Normal/Underweight(ref)				
Overweight[#]	0.64(0.47-0.88)	*0.01*	0.73(0.59-0.92)	*0.007*
Obese[#]	0.81(0.59-1.10)	*0.17*	0.71(0.56-0.89)	*0.004*
BMI (kg/m^2)	0.97(0.95-0.99)	*0.01*	0.93(0.92-0.95)	*<0.001*
BMI%	0.994(0.99-0.998)	*0.01*	1.00(0.99-1.01)	*0.14*
HOMA1-IR	1.02(0.95-1.09)	*0.67*	0.95(0.90-1.02)	*0.14*

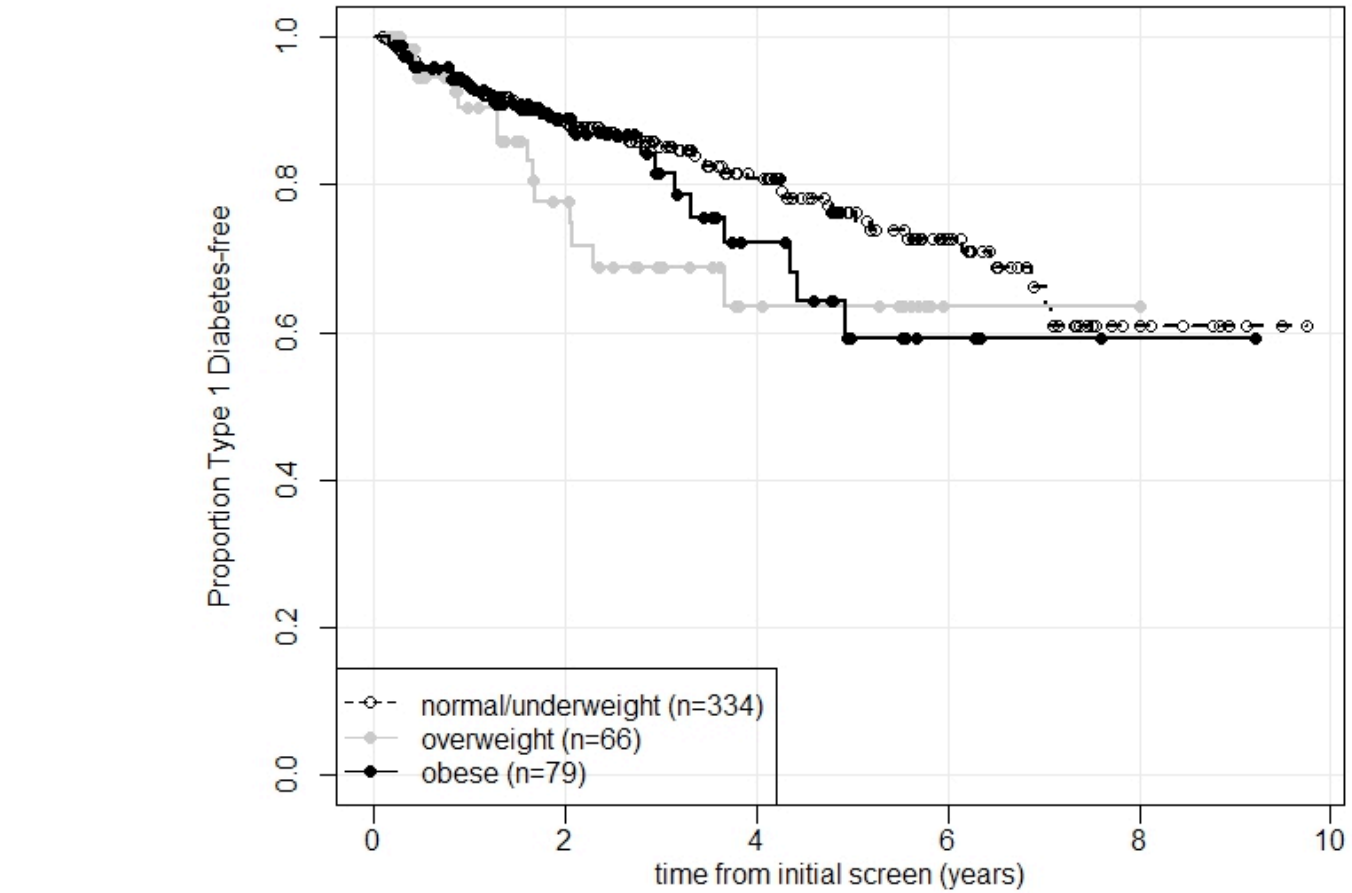
 # Obese defined as a BMI ≥ 30 and/or BMI% ≥ 95%, Overweight defined as BMI ≥ 25 and < 30 and/or BMI% ≥ 85% and < 95%. Reference group defined as normal or underweight.

Supplemental Figure 1:



Supplemental Figure 1: Final Analyses Cohort. Non-diabetic first, second, or third-degree relatives of individuals with type 1 diabetes were screened for the presence of pancreatic islet Aabs in a step-wise fashion. Confirmed Aab positive (Aab+) individuals were invited to participate in longitudinal observation with either semi-annual or annual monitoring. A total of 134,937 eligible individuals were screened from 2001 through June 30, 2014. A total of 2,299 individuals were confirmed on repeat testing to be single Aab (GAD65, insulin, or IA-2/ICA512) positive, while a total of 2,960 individuals were identified to be multiple Aab+ (GAD65, insulin, IA-2/ICA512, ICA, or ZnT8). Analyses presented here focus on those who had at least one monitoring visit (1,310 single Aab+ and 1,897 multiple Aab+ subjects). Within the single Aab+ group, 288 subjects progressed to multiple Aab+ status, while 68 individuals progressed to diabetes. Within the multiple Aab+ group, 579 individuals progressed to T1D. PTP = Pathway to Prevention; T1D = Type 1 Diabetes; Aab+ = autoantibody-positive; Aab- = autoantibody-negative. **Indicates confirmed positivity of the same type of islet autoantigen.*

Supplemental Figure 2:



Supplemental Figure 2: Time to Type 1 Diabetes by BMI Group in Subjects 13-20 years of age. Kaplan-Meier plots of diabetes-free survival in 532 PTP Participants 13-20 years of age stratified by BMI category. BMI category divisions included underweight (BMI <18.5 and/or BMI% <5%) combined with normal weight subjects (BMI ≥ 18.5 kg/m^2 and < 25 kg/m^2 and/or BMI percentile ≥ 5% and < 85%); overweight (BMI ≥ 25 kg/m^2 and < 30 kg/m^2 and/or BMI percentile ≥ 85% and < 95%); and obese (BMI ≥ 30 kg/m^2 and/or BMI percentile ≥95%). The HR of obese subjects is 2.03 (95% CI 1.00-4.10); p=0.049 vs. normal/underweight, adjusted for age at initial screen, gender, HLA risk, relationship to proband, race, and number of Aabs at initial screen. The HR of overweight vs. normal/underweight is 1.35 (95% CI 0,69-2.64); p=0.38, whereas the HR of obese vs. non-obese is 1.92 (95% CI 0.96-3.84); p=0.064.

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